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(FILE 'HOME' ENTERED AT 13:34:31 ON 31 MAY 2001)

INDEX 'ADISALERTS, ADISINSIGHT, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, ...' ENTERED AT 13:34:41 ON 31 MAY 2001

SEA EXCITATO? OR EXCITOTO?

310	FILE ADISALERTS
252	FILE ADISINSIGHT
230	FILE AGRICOLA
25	FILE ANABSTR
839	FILE AQUASCI
169	FILE BIOBUSINESS
22	FILE BIOCOMMERCE
38921	FILE BIOSIS
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2119	FILE BIOTECHNO
725	FILE CABA
1048	FILE CANCERLIT
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3755	FILE DRUGU
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314	FILE EMBAL
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18531	FILE ESBIOBASE
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125	FILE GENBANK
19	FILE HEALSAFE
445	FILE IFIPAT
2351	FILE JICST-EPLUS
10	FILE KOSMET
13666	FILE LIFESCI
10	FILE MEDICONF
33213	FILE MEDLINE
120	FILE NIOSHTIC
337	FILE NTIS
106	FILE OCEAN
14891	FILE PASCAL
46	FILE PHAR
157	FILE PHIN

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            25703   FILE SCISEARCH
                5   FILE SYNTHLINE
             7783   FILE TOXLINE
            15968   FILE TOXLIT
             2061   FILE USPATFULL
              567   FILE WPIDS
              567   FILE WPINDEX
L1               QUE EXCITATO? OR EXCITOTO?
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     FILE 'BIOSIS, MEDLINE, EMBASE, SCISEARCH, CAPLUS' ENTERED AT 13:36:09 ON
     31 MAY 2001
L2           389 S L1 AND (JNK OR C-JUN)
L3            16 S L2 AND (JNK3 OR JNK-3)
L4             6 DUP REM L3 (10 DUPLICATES REMOVED)
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              334   FILE PROMT
            25703   FILE SCISEARCH
                5   FILE SYNTHLINE
             7783   FILE TOXLINE
            15968   FILE TOXLIT
             2061   FILE USPATFULL
              567   FILE WPIDS
              567   FILE WPINDEX
L1                  QUE EXCITATO? OR EXCITOTO?
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     FILE 'BIOSIS, MEDLINE, EMBASE, SCISEARCH, CAPLUS' ENTERED AT 13:36:09 ON
     31 MAY 2001
L2           389 S L1 AND (JNK OR C-JUN)
L3            16 S L2 AND (JNK3 OR JNK-3)
L4             6 DUP REM L3 (10 DUPLICATES REMOVED)
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=> d l4 ibib ab 1-6

L4 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 2001:244841 BIOSIS
DOCUMENT NUMBER: PREV200100244841
TITLE: Kainate receptor activation induces mixed lineage kinase-mediated cellular signaling cascades via post-synaptic density protein 95.
AUTHOR(S): Savinainen, Anneli; Garcia, Elizabeth P.; Dorow, Donna; Marshall, John; Liu, Ya Fang (1)
CORPORATE SOURCE: (1) Northeastern University, 360 Huntington Ave., 312 Mugar Hall, Boston, MA, 02115: yafliu@lynx.neu.edu USA
SOURCE: Journal of Biological Chemistry, (April 6, 2001) Vol. 276, No. 14, pp. 11382-11386. print.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Kainate receptor glutamate receptor 6 (GluR6) subunit-deficient and **c-Jun** N-terminal kinase 3 (**JNK3**)-null mice share similar phenotypes including resistance to kainite-induced epileptic seizures and neuronal toxicity (Yang, D. D., Kuan, C-Y., Whitmarsh, A. J., Rincon, M., Zheng, T. S., Davis, R. J., Rakis, P., and Flavell, R. (1997) Nature 389, 865-869; Mulle, C., Seiler, A., Perez-Otano, I., Dickinson-Anson, H., Castillo, P. E., Bureau, I., Maron, C., Gage, F. H., Mann, J. R., Bettler, B., and Heinemmann, S. F. (1998) Nature 392, 601-605). This suggests that **JNK** activation may be involved in GluR6-mediated **excitotoxicity**. We provide evidence that post-synaptic density protein (PSD-95) links GluR6 to **JNK** activation by anchoring mixed lineage kinase (MLK) 2 or MLK3, upstream activators of **JNKs**, to the receptor complex. Association of MLK2 and MLK3 with PSD-95 in HN33 cells and rat brain preparations is dependent upon the SH3 domain of PSD-95, and expression of GluR6 in HN33 cells activated **JNKs** and induced neuronal apoptosis. Deletion of the PSD-95-binding site of GluR6 reduced both **JNK** activation and neuronal toxicity. Co-expression of dominant negative MLK2, MLK3, or mitogen-activated kinase kinase (MKK) 4 and MKK7 also significantly attenuated **JNK** activation and neuronal toxicity mediated by GluR6, and co-expression of PSD-95 with a deficient Src homology 3 domain also inhibited GluR6-induced **JNK** activation and neuronal toxicity. Our results suggest that PSD-95 plays a critical role in GluR6-mediated **JNK** activation and **excitotoxicity** by anchoring MLK to the receptor complex.

L4 ANSWER 2 OF 6 MEDLINE
ACCESSION NUMBER: 2001197795 MEDLINE
DOCUMENT NUMBER: 21136582 PubMed ID: 11238729
TITLE: Direct inhibition of **c-Jun** N-terminal kinase in sympathetic neurones prevents **c-jun** promoter activation and NGF withdrawal-induced death.
AUTHOR: Eilers A; Whitfield J; Shah B; Spadoni C; Desmond H; Ham J
CORPORATE SOURCE: Eisai London Research Laboratories, University College London, London, UK.

SOURCE: JOURNAL OF NEUROCHEMISTRY, (2001 Mar) 76 (5) 1439-54.
Journal code: JAV; 2985190R. ISSN: [redacted]2-3042.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered PubMed: 20010312
Entered Medline: 20010405

AB **c-Jun** N-terminal kinases (**JNKs**) regulate gene expression by phosphorylating transcription factors, such as **c-Jun**. Studies with **JNK**: knockout mice suggest that **JNK** activity may be required for **excitotoxin** -induced apoptosis in the adult hippocampus and for apoptosis in the developing embryonic neural tube. Here we investigate the role of **JNKs** in classical neurotrophin-regulated developmental neuronal death by using nerve growth factor (NGF)-dependent sympathetic neurones. In this system, NGF withdrawal leads to an increase in **JNK** activity, an increase in **c-Jun** protein levels and **c-Jun** N-terminal phosphorylation before the cell death commitment point, and **c-Jun** activity is required for cell death. To inhibit **JNK** activity in sympathetic neurones we have used two different **JNK** inhibitors that act by distinct mechanisms: the compound SB 203580 and the **JNK** binding domain (JBD) of **JNK** interacting protein 1 (JIP-1). We demonstrate that **JNK** activity is required for **c-Jun** phosphorylation, **c-jun** promoter activation and NGF withdrawal-induced apoptosis. We also show that ATF-2, a **c-Jun** dimerization partner that can regulate **c-jun** gene expression, is activated following NGF deprivation. Finally, by co-expressing the JBD and a regulatable **c-Jun** dominant negative mutant we demonstrate that **JNK** and AP-1 function in the same pro-apoptotic signalling pathway after NGF withdrawal.

L4 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 2000:509978 BIOSIS
DOCUMENT NUMBER: PREV200000509978
TITLE: **c-Jun** and the transcriptional control of neuronal apoptosis.
AUTHOR(S): Ham, Jonathan (1); Eilers, Andreas; Whitfield, Jonathan; Neame, Stephen J.; Shah, Bina
CORPORATE SOURCE: (1) Cancer Biology and Molecular Haematology Unit, Institute of Child Health, University College London, 30 Guilford Street, London, WC1N 1EH UK
SOURCE: Biochemical Pharmacology, (15 October, 2000) Vol. 60, No. 8, pp. 1015-1021. print.
ISSN: 0006-2952.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB There has been considerable interest in the molecular mechanisms of apoptosis in mammalian neurons because this form of neuronal cell death is important for the normal development of the nervous system and because inappropriate neuronal apoptosis may contribute to the pathology of human neurodegenerative disease. The aim of recent research has been to identify the key components of the cell death machinery in neurons and understand how the cell death programme is regulated by intracellular signalling pathways activated by the binding of neurotrophins or death factors to specific cell surface receptors. The aim of this commentary was to review research that has investigated the role of the Jun N-terminal kinase (**JNK**)/**c-Jun** signalling pathway in neuronal apoptosis, focusing in particular on work carried out with developing

sympathetic neurons. Experiments with sympathetic neurons cultured in vitro, as well as with cerebellar granule neurons and differentiated PC12 cells, have demonstrated that **JNK/c-Jun** signalling can promote apoptosis following survival factor withdrawal. In addition, experiments with **Jnk**(-/-) knockout mice have provided evidence that **Jnk3** may be required for apoptosis in the hippocampus in vivo following injection of kainic acid, an **excitotoxin**, and that Jnk1 and Jnk2 are required for apoptosis in the developing embryonic neural tube. However, in the embryonic forebrain, Jnk1 and Jnk2 have the opposite function and are necessary for the survival of developing cortical neurons. These results suggest that **JNKs** and **c-Jun** are important regulators of the cell death programme in the mammalian nervous system, but that their biological effects depend on the neuronal type and stage of development.

L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:737080 CAPLUS
DOCUMENT NUMBER: 131:346549
TITLE: Method to identify **JNK**- and MLK-kinase inhibiting compounds for prevention of neuron death
INVENTOR(S): Liu, Ya Fang
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958982	A1	19991118	WO 1999-US10416	19990512
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1078268	A1	20010228	EP 1999-922972	19990512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-85439 P 19980514
US 1998-156367 A1 19980917
WO 1999-US10416 W 19990512

AB Methods are described for identifying compds. that inhibit **JNK** and MLK kinase activity as drugs for treating a mammal susceptible to or having a neurol. condition. Methods are also disclosed for preventing neuronal cell death and treating neurol. conditions that involve neuronal cell death, particularly neurodegenerative diseases characterized by glutamine- or kainate-mediated toxicity, e.g. Huntington's disease and Alzheimer's disease.

REFERENCE COUNT: 2
REFERENCE(S): (1) Dickens, M; Science 1997, V277, P693 CAPLUS
(2) University of Massachusetts; WO 9918193 A 1999 CAPLUS

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:244741 CAPLUS
DOCUMENT NUMBER: 130:265957
TITLE: **JNK3** function in **excitotoxicity** and its use in treating related disorders and screening for modulators
INVENTOR(S): Davis, Roger J.; Flavell, Richard A.; Rakic, Pasko; Whitmarsh, Alan J.; Kuan, Chia-Yin; Yang, Di
PATENT ASSIGNEE(S): University of Massachusetts, USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918193	A1	19990415	WO 1998-US20904	19981005
W: AU, CA, JP, KR				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9911860	A1	19990427	AU 1999-11860	19981005
EP 1027429	A1	20000816	EP 1998-954937	19981005
R: DE, GB				

PRIORITY APPLN. INFO.: US 1997-60995 P 19971003
WO 1998-US20904 W 19981005

AB The **c-Jun** N-terminal kinase (**JNK**) group of MAP kinases are activated by exposure of cells to environmental stress. The role of **JNK** in the brain was examd. by targeted disruption of the gene that encodes the neuronal isoform **JNK3**. **JNK3** plays a role in stress-induced seizure activity, AP-1 transcriptional activation, and kainate-induced apoptosis of hippocampal neurons. Mice lacking the **JNK3** gene develop normally and are resistant to **excitotoxic** damage. Thus, **JNK3** is a mediator of kainate-glutamate **excitotoxicity** and a target for limiting or preventing **excitotoxic** damage. Methods of screening for mols. and compds. that decrease **JNK3** expression or activity are described. Such mols. or compds. are useful for treating disorders involving **excitotoxicity** such as seizure disorders, Alzheimer's disease, Huntington disease, Parkinson's disease, and ischemia.

REFERENCE COUNT: 6
REFERENCE(S):
(1) Carboni; Neuroscience 1997, V80(1), P147 CAPLUS
(3) Gupta; The EMBO Journal 1996, V15(11), P2760 CAPLUS
(4) Lander; The Journal of Biological Chemistry 1996, V271(33), P19705 CAPLUS
(5) Lo; The Journal of Biological Chemistry 1996, V271(26), P15703 CAPLUS
(6) Yang; Proceedings of the National Academy of Sciences USA 1997, V94, P3004 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
ACCESSION NUMBER: 1997:518184 BIOSIS
DOCUMENT NUMBER: PREV199799817387
TITLE: Absence of **excitotoxicity**-induced apoptosis in the hippocampus of mice lacking the **Jnk3** gene.
AUTHOR(S): Yang, Derek D.; Kuan, Chia-Yi; Whitmarsh, Alan J.; Rincon, Mercedes; Zheng, Timothy S.; Davis, Roger J.; Rakic, Pasko; Flavell, Richard A. (1)
CORPORATE SOURCE: (1) Sect. Immunobiol., Yale Univ. Sch. Med., New Haven, CT 06510 USA
SOURCE: Nature (London), (1997) Vol. 389, No. 6653, pp. 865-870. ISSN: 0028-0836.
DOCUMENT TYPE: Article
LANGUAGE: English

AB **Excitatory** amino acids induce both acute membrane depolarization and latent cellular toxicity, which often leads to apoptosis in many neurological disorders. Recent studies indicate that glutamate toxicity may involve the **c-Jun** amino-terminal kinase (**JNK**) group of mitogen-activated protein (MAP) kinases. One member of the **JNK** family, **Jnk3**, may be required for stress-induced neuronal apoptosis, as it is selectively expressed in the nervous system. Here we report that disruption of the gene encoding **Jnk3** in mice caused the mice to be resistant to the **excitotoxic** glutamate-receptor agonist kainic acid: they showed a

reduction in seizure activity and hippocampal neuron apoptosis was prevented. Although application of kainic add imposed the same level of noxious stress, the phosphorylation of **c-Jun** and the transcriptional activity of the AP-1 transcription factor complex were markedly reduced in the mutant mice. These data indicate that the observed neuroprotection is due to the extinction of a **Jnk3**-mediated signalling pathway, which is an important component in the pathogenesis of glutamate neurotoxicity.